ably led to too low results and it is significant that those so obtained were lower than those obtained when iodometric methods were used. See 'The Iodometric Determination of Sulfur Dioxide and the Sulfites,' J. B. Ferguson, *J. Amer. Chem. Soc., Easton, Pa.*, **39**, 1917, (364).

[6] Thomsen's value is 71080. (Thomsen, *Thermische Untersuchungen*, **2**, p. 251)

[7] This value agrees with that derived from some preliminary investigations by M. Randall on sulfur and water (*Thesis, Mass. Inst. Tech., Boston*, 1912) and also with that obtained by Lewis and Bichowsky in a more complete investigation carried out at higher temperatures (private communication).

PHYSIOLOGICAL EFFECT ON GROWTH AND REPRODUCTION OF RATIONS BALANCED FROM RESTRICTED SOURCES

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Our early work[1] on the nutrition of herbivora with restricted rations demonstrated clearly the inadequacy of the accepted theory as to what constitutes a balanced or complete ration. Up to that time total protein—without reference to quality—energy, and ash materials were considered the essentials of a ration. The latter, however, occupied no position in the mathematical expression of the standards developed. The standards have been stated only in terms of total digestible protein and energy. It is, however, probably true that in a practical sense, and with the generally accepted knowledge of the quality of materials accumulated from a long and varied experience, that such standards have had and will continue to have very great value; but their limitations are also made evident by this earlier work and are emphasized by what we have since done. Within the past few years our knowledge[2] of the essentials of a ration have expanded and today we would consider a ration complete and efficient only when it contained protein of adequate quantity and quality, adequate energy, ash materials in proper quantity and proportion and two factors of unknown constitution (vitamines), designated from this laboratory[3] fat soluble A and water soluble B.

In addition to the above normal factors there may be introduced with natural food-stuffs the important factor of toxicity.[4] This can be wholly absent or so mild in its effects as to be entirely obscured when the other essentials of a ration are at an optimum adjustment; or with fair adjustment it may only reveal its effects when the ration is continued over a very long time and the animal involved in the extra strains of reproduction and milk secretion. This resistance to toxicity

is very materially increased through a proper adjustment of the normal factors of nutrition.

With this recognition of all the normal factors for adequate nutrition there must not simultaneously arise a desire for a mathematical expression of these factors in feeding standards. It is doubtful if this can ever be done, at least for certain of them. For example, the rôle of the mineral nutrients is so varied, including such widely separate functions as construction and control through antagonism as to make it seem futile to attempt an expression of absolute requirements when natural foods, with their diversity of mineral content, are involved. Even the recognition of differences in the quality of proteins and their relation to nutrition[5] will make it more difficult to continue expressing protein requirements in exact quantities than before the development of such knowledge; and what can be said of the quantitative requirements of fat soluble A and water soluble B and their supply in feeding materials?

All these developments of the last few years emphasize the need of a thorough study of the contributing nutritive factors of a *single* food stuff, and in the state of our present knowledge such information will be secured only by physiological tests, involving the animal in reproduction and milk secretion. A contributing factor by a natural food may at times be in the nature of toxicity and this may serve as a harmful and abnormal factor. As such knowledge develops and it becomes clear that this or that single food material will supply adequately the normal nutritive factors, not measurable by any quantitative chemical method, such as fat soluble A, water soluble B, or mineral nutrients, we will return with more confidence to the mathematical standard that only involves the energy and protein supply of that single food material. This confidence in the expressed quantities of energy and protein available in a food-stuff will rest upon the definite information that they become physiological effective only when they form part of a ration which carries one or a number of food-stuffs supplying adequately the other nutritive factors. With such an understanding the feeding standards developed on the energy-protein basis would continue to be theoretically sound and of very great practical value. As illustrative of our position, and taken from our own experience with wheat grain feeding we would feel reasonably safe if a wheat grain ration, based on protein and energy and to be fed continuously to a growing herbivorous animal, was built around alfalfa hay; less safe if built around corn stover, and fearful of disaster should the roughage used be wheat straw.

In our earlier experiments a 'balanced' ration from the wheat plant

gave fair growth, but complete failure in reproduction with heifers, while a 'balanced' ration from the corn plant was successful.

In our attempts to locate the trouble in the all wheat ration, wheat grain—wheat straw—we have fed rations made up of corn grain and wheat straw. Here the offspring were weak and often born dead. When to that same ration, however, a suitable salt mixture was added so that the ash content of the ration was like that of the all corn ration perfect offspring resulted. This would clearly indicate that one of the deficiencies of an all wheat plant ration was a proper salt mixture. When, however, the corn grain in the above ration was displaced by the wheat grain and the ration consisted of wheat grain—wheat straw and salts, disaster again resulted, which showed the presence of another disturbing factor in the wheat grain. Calves born by mothers upon this ration showed peculiar deflections of the head, inability to get up and suckle the mother, and in most cases have died within a few hours after birth.

These experiments indicate that in the all wheat plant ration there were two factors operative against normal nutrition, namely, a poor salt mixture and inherent toxicity of the wheat grain. When the wheat grain was coupled with corn stover we have sometimes met with success and sometimes with failure in the character of the offspring. With strong mothers it appears that the corn stover may become an 'antidote' and thereby furnish sufficient of all the normal factors of nutrition so as to enable the animal to reproduce normally.

The possibility of the toxicity being destroyed by heat was also investigated and baked wheat was fed with corn stover. This had no effect whatever in improving the wheat kernel.

In other cases the wheat grain-corn stover ration had butter fat added to it for the purpose of supplying plentifully the growth promoting—factor-fat soluble A—now known to be necessary for growth and supplied abundantly in butter fat. It was thought possible that the wheat grain-wheat straw ration was somewhat deficient in this material. Butter fat additions, however, did not uniformly improve the ration. We had a number of failures in reproduction, and also a number of successes with its use. This would again emphasize the probability of the presence of a toxic substance in the wheat grain.

When, however, the wheat grain was mixed with a legume hay, such as alfalfa, so that the latter formed but 20% of the ration, we have had perfect success in all cases in the production of normal offspring, at least for the first gestation. The improvement resulting from the use of the alfalfa must lie in introducing into the ration a better salt mix-

ture, perhaps a better protein mixture, and an abundance of growth promoting substances, all of which may contribute toward making it possible for the cell to destroy or resist the action of the toxic substance introduced. However, in the second gestation period on the same ration—wheat grain, wheat straw, alfalfa hay, the calves were weak, and in one case blind, but lived. This is extremely interesting as illustrating the cumulative effect of this toxicity.

Where corn stover was wholly substituted for the wheat straw we had a number of successes and also a number of failures in the first gestation period. Apparently this roughage was not as effective as an 'antidote' to the toxicity as the legume hay.

We had thought it possible in our earlier work that the acidity of the wheat ration was an important factor in the results recorded. It was true that the urine of the all-wheat plant fed animals showed a slight acidity to litmus due to a low intake of bases in the ration. If this were an important factor in our results then the successful corn ration might be disturbed with acids and give us results similar to the wheat ration. This however, we found not to be the case; for when to an all corn ration there were added mineral acids, such as sulphuric and phosphoric acids, in such proportions as to make the acidity of the urine of a degree similar to that of a wheat-wheat straw fed animal, the offspring were strong and normal in every respect. Even the addition of a high proportion of magnesium salts to a corn ration did not disturb in any way its power of producing normal offspring.

The results detailed above indicate clearly that wheat grain contains a toxic material, and later work has shown that this is very prominent in the embryo of the seed. When wheat embryo is imposed on corn stover so as to bring into the ration seven to eight times the amount of embryo that would be introduced when feeding whole wheat, the result is likely to be an early abortion. The calf is now dropped at six to eight months; this demonstrates that the increased mass of the toxic material produces this disturbance at a somewhat more rapid rate. This result was particularly apt to occur where no other grain was used with the embryo. With both corn meal and corn stover in the ration the detrimental effect of the wheat embryo was nullified, at least for a single gestation period.

It is an interesting fact that in the wheat milling industry the embryo passes into wheat bran in small amounts but in much greater quantities in wheat middlings. The wheat flour that is used for bread making has the least content of embryo of any of the wheat by-products.

In an attempt to obtain an anatomical picture of the condition re-

FIG. 1. CALF FROM COW 562

Wheat embryo 3 parts, corn starch 4 parts, corn stover 7 parts. The embryo of the wheat grain carries a considerable mass of toxicity. Massing this in the ration brought on early abortion with a gestation period of six to seven months. This ration was a so-called 'balanced' ration.

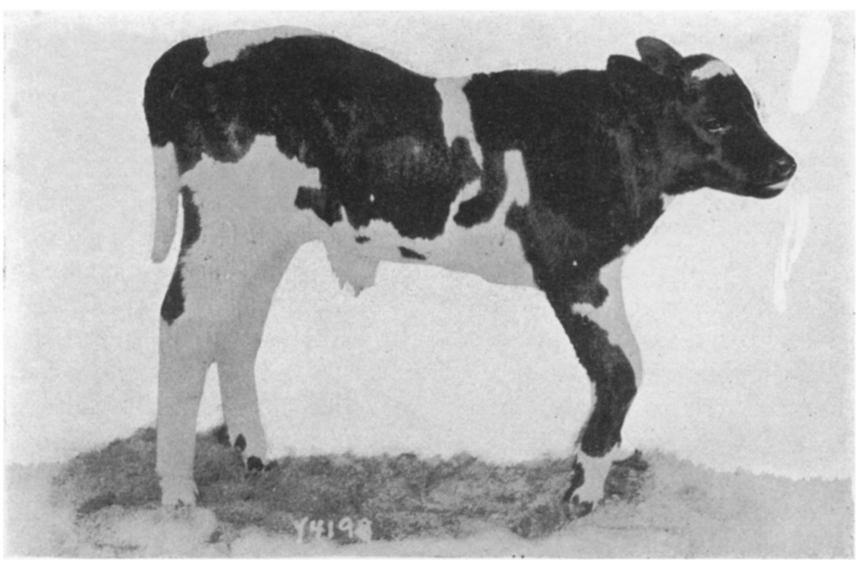

FIG. 2. CALF FROM COW 648

Second gestation on a ration of wheat grain 8 parts, wheat gluten 0.3 part, wheat straw 2.9 parts, alfalfa hay 2.9 parts. In the first gestation this cow produced a strong calf on this ration. In this second gestation period the calf was carried to full time, but was weak and was fed from a bottle; grew strong, but the front legs were weak and it stood for the first few days of its life on the first joints. *This calf was blind.* The mother remained in apparently good condition. This again illustrates the cumulative effect of the wheat toxicity.

sponsible for the physiological disturbances as already described, Dr. Bunting of the Medical School of the University, kindly consented to make a histological study of the tissues from a number of the abnormal calves. In general no striking lesions were revealed. Livers and kidneys showed some degeneration (hydropic) changes, but the nervous tissues gave the most evidence of the presence of an excessive amount of fluid—a condition of oedema. This histological picture was anal-

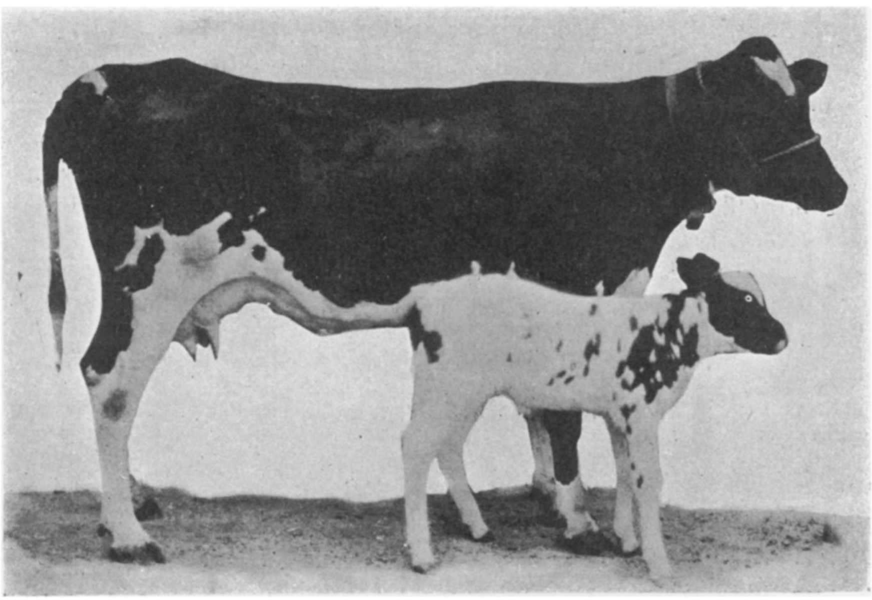

FIG. 3. COW 662 AND CALF

Successful reproduction in the presence of the embryo. A ration of corn meal 4 parts, corn starch 1 part, wheat embryo 2 parts, corn stover 7 parts. At least for the first gestation the 'antidotal' properties of corn meal and corn stover were sufficient to overcome the toxic effect of the wheat embryo. Without the corn meal and with only wheat embryo, starch, and corn stover in the ration reproduction would have been premature and the calf either dead or markedly undersize (see figure 1).

ogous to that of beri beri, the result of feeding polished rice, and it also simulated, if it was not identical, with that obtained from the spinal cord of pigs on certain rations as described in a previous publication.[4] The oedema was observed between the membranes covering the cord, around the blood vessels and around the nerve cells. In these instances the nerve cell and their nuclei were shrunken, the latter staining more intensely than normally. No abnomalities in medullation of the fibers of the cord as demonstrable by the Weigert stain were observed. While the observations did not point to anything especially characteristic it

is probable that the motor disturbances observed in the animals can be referred to the oedematous condition of the nervous tissues. The cause of beri beri is ascribed to the absence or deficiency of certain essential factors in the diet, particularly to water soluble B. In the case of excessive wheat feeding it would appear that the essential causal factor for disaster to growth and reproduction is a toxic substance which either interferes with the utilization of materials necessary for the full development of the nervous system of the animal or directly with the normal functioning of this tissue. This would account for the blindness observed in some of the heifers and also for the failure of muscular coordination apparent in the new born calves produced on rations of large whole wheat content.

It was also apparent that rations producing an early delivery of offspring would usually lead to a failure of the animal to remove properly the afterbirth, with its attending dangers of infection; and an overabundance of a material like wheat straw in a ration, owing to its low salt content, becomes an important factor in premature birth.

An observation in our experimental work of interest to veterinarians was the low resistance to other diseases of the mothers fed the wheat ration. In an outbreak of anthrax in the university herd the only losses to occur from this disease in our experimental herd were among the wheat grain fed animals.

The principle[5] laid down as to what factors must be present in a ration of natural origin in order that it becomes efficient for both growth and reproduction is well supported by these data. This principle postulates that there must be present efficient proteins, adequate energy, proper salt mixture, fat soluble A and water soluble B (vitamines) and an absence of toxicity or a toxicity of such mildness as to become inocuous in the presence of the other normal factors of nutrition. The presence of toxicity in the wheat kernel as the explanatory factor for these records rests not only upon the evidence secured with swine and rats but also on that presented here. *It is not a deficiency phenomenon.* A wheat grain, corn stover ration often failed, not only when used alone but when there was added to it the most likely limiting factor, fat soluble A, as butter fat.

The recognition of these normal factors of nutrition and the further recognition of the occurrence in apparently normal food-stuffs of substances of mild toxicity will be of immense advantage in arriving at an understanding of the oft reported troubles with farm animals which today are either not understood or their etiology wrongly assigned; and in the field of human nutrition the same principles will apply.

When a few years ago the corn crop of Nebraska failed to mature because of drought, but early rains had produced a bumper wheat crop it left many farmers with little to feed their breeding stock but wheat grain and certain roughages. In many cases where this was done the calves were born either dead or weak, with great financial losses to many breeders. No one would have suspected that the ration was a factor in these disasters, but it undoubtedly was the direct cause of the trouble.

When Dakota farmers, with their only roughage as wheat straw, try to build up an animal husbandry industry there is likely to arise trouble in reproduction with this class of animals unless other roughages with better salt mixtures are brought into the ration. We are informed that there is already much trouble with reproduction by cows in the Dakotas wherever much wheat straw is fed. Such facts as these must emphasize the importance of an understanding of all the factors of animal nutrition and in addition an understanding of all the factors contributed by any particular food-stuff. It should further emphasize how such studies can furnish the facts which will aid the animal feeder in avoiding the danger zones of his art. *We need more effort placed on the accumulation of information on the physiological behavior of feeding stuffs than on the attempts to bring out new mathematical expressions of feeding standards.*

These experiments further show the limitations of the theory of a 'balanced' ration as now expressed and indicate the very great importance of other factors besides protein and energy in the successful diet. It was indeed surprising to find that the common wheat kernel had a low toxicity; but such factors as toxicity, growth promoting substances of unknown nature, proper balance of salts, indicate how complex the problems of animal nutrition really are and how necessary it is that these factors be clearly exposed in order that we may place the various feeds in their proper category. We have pointed out how a material of low toxicity, such as the wheat kernel, may be used with success. A good roughage like a legume hay was an admirable 'antidote.' Even corn meal and a poorer roughage like corn stover served to offset the detrimental effects of a large mass of wheat embryo. This also illustrates how an adjustment of the normal factors of nutrition may conceal the presence of the detrimental factors.

It is important to keep constantly in mind that the disclosure of either a nutritive deficiency or the presence of an abnormal factor in a common natural food stuff should not necessarily condemn its use. It should, however, emphasize the need of combining it in the ration with

those other natural products which will either supply abundantly the deficiencies or act as an 'antidote' to any inherent toxicity.

[1] Hart, E. B., McCollum, E. V., Steenbock, H., and Humphrey, G. C., *Wisconsin Exp. Sta. Research Bull.* No. **17,** 1911.

[2] Stepp, W., *Zs. Biol., München*, **57,** 1912, (135) 62, 1913, (405); Hopkins, F. G., *J. Physiol.* **44,** 425, 1912; Funk, C., *Zs. Physiol. Chem.*, **88,** 1913; (352), **92,** 1914, (13); McCollum, E. V., and Davis, M., *J. Biol. Chem.*, **15,** 1913; (167), **23,** 1915, (231); Osborne, T. B. and Mendel, L. B. *Ibid.*, **15,** 1913, (311).

[3] McCollum, E. V., and Kennedy, C., *J. Biol. Chem.*, **24,** 1916, (491).

[4] Hart, E. B., and McCollum, E. V., *Ibid.*, **19,** 1914, (373); McCollum, E. V., and Simmonds, N., and Pitz, W., *Ibid.*, **25,** 1916, (105); Hart, E. B., Miller, W. C., and McCollum, E. V., *Ibid.*, **25,** 1916, (239).

[5] Hart, E. B., Miller, W. C., and McCollum, E. V., *Ibid.*, **25,** 1916, (239); McCollum E. V., Simmonds, N., and Pitz, W., *Ibid.*, **25,** 1916, (105).

WHAT DETERMINES THE DURATION OF LIFE IN METAZOA?

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1. It can be stated as a fact that most if not all organisms have a characteristic duration of life. To give extreme examples, many insects have a duration of life measured in weeks only, while the Californian sequoia has a duration of life of thousands of years, and in the human being the duration of life is proverbially three score and ten. The question arises: What determines this characteristic duration of life?

Bütschli was the first to point out that unicellular organisms have an unlimited duration of life and this idea has become very popular through Weismann. All recent researches support the correctness of this idea. As a consequence we are forced to the conclusion that natural death is a phenomenon found almost exclusively in organisms which are composed of different organs. The idea that natural death is connected with the compound character of organisms is supported by two facts; namely, first, the observation that a cutting will survive the whole plant, while the cutting if not separated would have died with the whole plant. By the method of cuttings the life of the individual plant can be prolonged apparently indefinitely.

The second fact is that if we take pains to transplant certain cells from an old organism successively to young organisms, these cells will outlive the original individual indefinitely—they are, in other words, immortal. The proof can only be furnished with the aid of marked cells and Leo Loeb selected for this purpose the cancer cell which is easily distinguishable from other cells by its rapid growth. He thus